No. 103,739. The Examiner is invited to review the pending claims in the '376 application.

As requested, the title of the present application has been amended in accordance with the Examiner's suggestion. Pending Claims 47-57 have been cancelled and replaced by new Claims 58-75. The new claims, directed to a reagent, i.e. a detection primer, are fully supported by the specification and correspond to the detection primer of the allowed method claims in the '376 application.

Claims 47-57 stand rejected under 35 U.S.C. § 112, ¶ 2. Claims 47-57 have been replaced by new Claims 58-75, which more clearly define the subject matter of the claimed invention. Moreover, the language of new independent Claim 58 clarifies the Examiner's concerns. The Examiner also noted that original Claims 49-57 (now Claims 61-69) are allowable over the art. In view of the amendment obviating the Section 112, ¶ 2 rejection, Claims 61-69 are allowable. Applicants respectfully request withdrawal of the rejections of all of the pending claims under 35 U.S.C. § 112, ¶ 2 in view of the amendments and remarks herein.

Claims 47 and 48 have been rejected under 35 U.S.C. § 103 as obvious in view of U.S. Patent No. 5,310,893 Erlich et al. (hereinafter "Erlich").

According to the Examiner, Erlich teaches: (1) primers useful for the amplification of target nucleic acids

(i.e., amplification primers) containing a variable nucleotide, such as a polymorphism/mutation (at col. 8); (2) primers are generated which have the property of hybridizing to the nucleic acid 5′ to the nucleotide in the target nucleic acid containing the variable nucleotide so that extension of the 3′ end of the primer results in the addition of a nucleotide complementary to the variable nucleotide; and (3) primers such as "DB01" (disclosed at cols. 29 and 30) that hybridize to the target nucleic acid so that the 3′ nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first and second nucleotide residue; and (4) that the 3′ residue of the DB01 primer flank the variable or mutated nucleotide, "C" and "G", adjacent to the primer.

In addition, the Examiner states: (1) Erlich teaches in Col. 4 that primers may be of 15 to 25 nucleotides in length; (2) Erlich does NOT teach a DB01 primer having an "attachment moiety" attached thereto through which the primer can be immobilized; however (3) Erlich teaches at col. 5 that primers useful for amplifying variable nucleotides can be modified so as to attach labels which can be used to capture the primer and facilitate immobilization of the primer onto a solid support.

According to the Examiner, it would have been

obvious to one skilled in the art at the time the invention was made to have modified the amplification primer of Erlich so as to have attached a moiety allowing for immobilization of the primer to have accomplished the expected advantage of generating a primer which could easily be immobilized for the rapid and efficient separation and isolation of the nucleic acids comprising the amplification primer from the other nucleic acids.

The Examiner apparently considers the amplification primer of Erlich as identical to the oligonucleotide detection step primer of the present invention, i.e., the claimed reagent. The Examiner relies on Erlich, col. 5, as teaching that additional amplification primers that hybridize with a portion of the target sequence may have labels attached thereto that are useful for capturing and immobilizing the amplified nucleic acids onto a solid support to justify the conclusion that "amplification primer" comprises an oligonucleotide and an attachment moiety. Erlich further teaches labelling of probes with radioactive and non-radioactive nucleotide triphosphate at cols. 11 and 26.

Applicants disagree. Applicants recognize that the amplification primers of Erlich and the amplification primers of the present invention are more or less identical. While Erlich does not exemplify the use of labeled

amplification primers as in the present invention, Erlich does suggest that such primers may be labeled (col. 5).

Where the Examiner is in error, however, is that the primers/probes that should be compared between Erlich and the present invention are Erlich's sequence specific oligonucleotide ("SSO") probes, such as the DB01 probe, and the detection step primers of the present invention. While both SSO and detection step probes/primers have the same function, i.e., to detect nucleotide variations at specific sites (within the sequence optionally amplified using an amplification primer), they work in different ways.

Erlich's SSO probes are designed to contain the variable nucleotide(s) within the oligonucleotide sequence of the probe itself. Thus, the Erlich method (and the corresponding reagents (primers/probes) for carrying out the method), by necessity, comprises a panel of SSO probes, specific for all of the variations to be detected. For example, the specific embodiments of Erlich's invention are a panel of HLA-specific SSO-probes, e.g., DP01. The SSO probes of Erlich are, in fact, the same as the ASO ("allele specific oligonucleotide") probes disclosed in the background to the present invention. See p. 5, lines 17-30 through p. 6, lines 1-24.

While Erlich does not specifically claim reagents for use in carrying out the method of the disclosed

invention, such reagents would be part of a kit comprising the following:

1. Amplification primers (optionally labelled) for amplification of a sequence segment containing the HLA DP locus (= nucleotide variations);

2. Optional (unlabeled) nucleotides for performing the amplification;

3. Optional solid support to collect the amplified target; and

4. A panel of labeled SSO probes (reagents) designed to hybridize to all nucleotide variations to be detected.

On the other hand, in the present invention, the reagent, i.e., the oligonucleotide detection step primer, is designed to hybridize to a segment of the target adjacent to the variable nucleotide to be detected. In other words, the detection step primer does not contain the variable nucleotide with the oligonucleotide sequence as does the SSO probe of Erlich. Utilizing a primer extension reaction (e.g., a PCR reaction) and labeled nucleotides, the primer is extended only if the added labeled nucleotide is complementary to the variable nucleotide, with the formed extension product being labeled.

The differences between the present invention and that of Erlich may be better understood by reference to the

attached figure, which schematically represents kits comprising reagents (i.e., probes/primers) according to Erlich and the present invention.

Furthermore, immobilization of the primer by the use of an attachment moiety in the present invention does not produce the "expected" advantage anticipated by the Examiner. The Examiner states that the use of an attachment moiety would be expected to accomplish the advantage of generating a primer which could easily be immobilized for the rapid and efficient separation and isolation of the nucleic acids comprising the amplification primer from the other nucleic acids. Here, the immobilization works as a second sorting mechanism to allow simultaneous detection of different target sites at different points in the genome. There is no need to separate the primer from the other nucleic acids because detection is not occurring as a result of amplification. Detection is occurring as a result of the use of labeled chain terminating nucleotide triphosphates that will bind if complimentary to the specific nucleotide at each of the predetermined positions in the same genome adjacent to a host of distinct detection primer attached to separately identifiable solid supports.

In the claims as amended, it is clear that the detection primer of the invention is used to form an extension product, said extension product being the means by

which the claimed reagent detects the variable nucleotide and that the detection is not occurring by amplification. It is therefore a leap of logic from the disclosure of Erlich, i.e., the existence of amplification primers, to render obvious the detection primers of the present invention that allow for the surgical detection of multiple generic variation simultaneously.

In view of the amendments to the claims and the remarks herein, applicants respectfully request reconsideration and allowance of pending Claims 58-75.

Respectfully submitted,

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Enclosures
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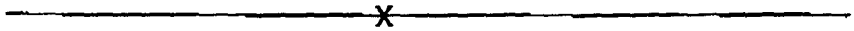
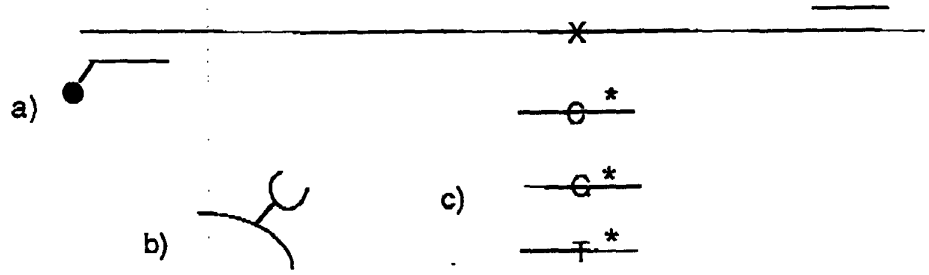
Kits for detecting one variable nucleotide X, which can be G, C or A



1) According to Erlich:
   a) optionally labelled amplification primers
   b) solid support for collecting the amplified target sequence
   c) a panel of three SSO-probes labelled for detection purposes



2) According to the present application:
   a) optionally labelled amplification primers
   b) solid support for collecting the amplified target sequence
   c) one detection step primer (optionally labelled)
   d) three labelled nucletides for detecting the variation